

NO: 2, residues 1-348 of SEQ ID NO: 3, residues 73-561 of SEQ ID NO: 4, and residues 70-558 of SEQ ID NO: 5.

107. (Amended) The method of claim 1, wherein said neuronal cells are selected from [the group consisting of] motor neurons, cholinergic neurons, dopaminergic neurons, [serotenergic] serotonergic neurons and peptidergic neurons.

### **REMARKS**

Claims 1, 42-50, 69, 70, 76-80, 82-86, 93, 95-100, 102-104, and 107-110 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-3. Applicants note that claims 42-48, 78, and 79 are withdrawn as being directed to a non-elected invention. Applicants point out that these claims are dependent on, and thereby linked by, claim 1, and upon allowance of this linking claim, the restriction requirement must be withdrawn pursuant to MPEP 809. Similarly, claims generic to patentably distinct species must be considered upon allowance of a generic claim pursuant to MPEP 809.02(b).

4. Applicants have amended the "Related Applications" paragraph to perfect the priority claims until 35 U.S.C. §120.

5. Applicants have amended the specification to include sequence listing designations at appropriate locations. Applicants submit that the specification is now in compliance with the sequence listing requirements.

6. Applicants have corrected the dependency of claim 93 to overcome the Examiner's objection.

7-8. Claims 1, 49, 50, 69, 70, 76, 77, 80-86, 96-100, 102-104, and 107-110 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-13 of copending Application No. 08/462,386. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

9-10. Claims 1, 49, 50, 69, 70, 76, 77, 80-86, and 96-98 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended claims 1, 49, and 77 as suggested by the Examiner. Applicants submit that the scope of these claims is not narrowed by this amendment.

Although Applicants maintain that the term *hedgehog* polypeptide is adequately described in the specification to allow one of ordinary skill in the art to comprehend the metes and bounds of this term, Applicants have amended claims 1, 49, and 50 to identify the *hedgehog* polypeptide in relationship to particular sequences.

Applicants have amended claim 80 to clarify the nature of the effect of the naturally occurring hedgehog protein, and have cancelled claim 81. Applicants submit that one of ordinary skill in the art would readily be able to determine the effect of a naturally occurring *hedgehog* protein on one or more of growth, differentiation, and survival of neuronal cells, and compare this effect with that of the recited *hedgehog* protein. Accordingly, Applicants submit that this amendment overcomes the Examiner's rejection of claim 80. Applicants have cancelled claim 81 solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Claim 83 has been amended to recite particular conditions for measuring hybridization, as recited in the specification on page 29. Nevertheless, Applicants maintain that one of skill in the art can readily determine stringent hybridization conditions, and that specifying particular conditions is not required for compliance with 35 U.S.C. § 112, second paragraph.

Claim 99 has been amended to overcome the Examiner's rejection of this claim. Applicants submit that the scope of the claim is not narrowed by this amendment.

For the reasons provided above, Applicants submit that the pending claims are in full compliance with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

11-12. Claim 81 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants have cancelled claim 81, as noted above, thereby obviating this rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

13. Claims 1, 49, 50, 69, 70, 76-77, 80, 82-86, 96-104, and 107-110 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action points to page 26 as indicating that Applicants have not provided sufficient guidance as to what variant sequences of naturally occurring hedgehog polypeptides can be successfully employed in the claimed methods. However, several other pages in the specification provide extensive guidance that would permit the skilled artisan to prepare many variant sequences which would be expected to operate in the presently claimed methods. On page 25, lines 16-24, the specification guides the skilled artisan in selecting suitable 19 kD fragments. Pages 28-29 point to particular fragments that can be employed in the claimed methods. The figures include several sequence alignments and consensus sequences useful for gauging the amenability of a particular amino acid to substitution. In light of this disclosure, Applicants submit that the statement in the Office Action that "trial and error experimentation" would be required to identify suitable active variants or fragments. Mother Nature herself has performed the background research that would make such experimentation 'undue'. By demonstrating which residues are conserved and which are variable throughout diverse organisms such as mice, humans, zebrafish, and chickens, Applicants have provided ample guidance to allow the rapid identification by one of skill in the art of suitable variants and fragments of the sequences disclosed.

The Office Action further suggests, implicitly, that only Sonic hedgehog sequences would be expected to be effective in the claimed methods, but fails to provide facts or reasoning

supporting this assumption. Applicants respectfully remind the Examiner that the Federal Circuit recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of the Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants.

Nevertheless, Applicants direct the Examiner's attention to the references provided herewith as Exhibit A. Takabatake et al., *FEBS Letters* **1997**, *41*, 485-489, note in the abstract that "*Dhh* was detected in the neural retina", indicating a connection between neural tissue and this homolog of *Shh*. Mirsky et al., *Ann. N. Y. Acad. Sci.* **1999**, *883*, 196-202, additionally point out that *Dhh* is detected in Schwann cells (Introduction, pp. 197-198), and that Schwann cells apparently provide signals crucial to neuronal survival and differentiation, further underscoring this relationship. Umehara et al., *Am. J. Hum. Genet.* **2000**, *67*, 1302-1305, demonstrate that mutations to *Dhh* apparently cause nerve abnormalities (see page 1304, left column). Parmantier et al., *Neuron* **1999**, *23*, 713-724, provide further results relating to the relationship between *Dhh* and nerve development.

Applicants further point out that Chang et al., *Development* **1994**, *120*, 3339-3353, indicates that Hhg-1, a mouse Sonic hedgehog gene, functions in *Drosophila* in a manner similar to the native *Drosophila* hedgehog protein, as described on pages 3344-3347, despite the fact that these polypeptides are only approximately 46% identical. Given that Chang et al. found that Hhg-1 and *Drosophila* *hedgehog*, though more than 30% divergent in the biologically active N-terminus and more than 50% divergent overall, showed comparable biological activity, Applicants submit that *Desert*, *Indian*, and *Sonic hedgehog* proteins would all be expected to have similar biological effects on neural cells, consistent with the teachings of the present specification, and no undue experimentation would be required to practice the claimed methods throughout their scope. For the reasons set forth above, Applicants submit that the present claims

are fully enabled and supported by the specification as filed. Reconsideration and withdrawal of this rejection is respectfully requested.

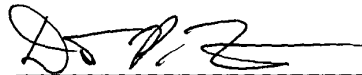
#### **CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

Date: July 18, 2001

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